

REMARKS

Claims 1, 2, 4-17, 24-27, 29, 30 and 34-36 were pending in the application. Of these, claims 24-27, 29, 30 and 34-36 were withdrawn from consideration.

Claims 1, 2 *and* 4-17 were examined and rejected.

The following active claims are being amended: 1, 2, 6, 7, 8, 9, 11 and 14. In addition, withdrawn claims 24 and 25 are being amended.

The following claims are being canceled herein: 4, 5, 10, 12, 13, 15, 16, 26, 27-30 and 34-36.

Thus, claims 1, 2, 6, 7, 9, 11, 14 and 17 are active and under examination while claims 24 and 25 remain withdrawn.

Support for some of the amendments is specifically discussed below. Other amendments are supported by the original claims and throughout the specification.

None of the amendments introduces new matter and their entry is requested. The Applications is now in condition for allowance which is respectfully requested.

I. Priority

The Office has reminded Applicants that a specific reference to a prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet.

Applicants are submitting herewith an Application Data Sheet that shows the claimed priority, thereby complying with the above rule.

II. Objections to Oath/Declaration

The oath or declaration was found to be defective because: It does not identify the citizenship of each inventor (due to a clerical error, Applicants citizenship was listed as "British Columbia" instead of "Canada")

Applicants submit herewith a **Substitute Declaration** that corrects this error.

III. Claim Objections

Claim 16 was objected to because of several different informalities.

With the cancelation of claim 16, this objection is not moot.

{Below, Applicants occasionally intersperse their observations and comments between sections that describe the Office's analysis. These remarks appear in a different font, Arial (vs. Times New Roman for the Office Action description)) and are indented, italicized and enclosed in 'braces' ({}). Following this are separate more detailed sections setting forth Applicants' response (reverting to Times New Roman font)}.

IV. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 2, 4, 6-8, and 10-16 were rejected as being indefinite for the reasons given below.

Claims 2, 4, and 6-8: “the polymorphic site” in claim 2 (from which claims 4 and 6-8 depend) lacks antecedent basis in claim 1.

Claim 4: insufficient antecedent basis for the language “the polymorphic site in linkage disequilibrium with position 5318 has...”; unclear as to how claim 4 might further limit its parent claims (as those claims no longer encompass polymorphic sites in linkage disequilibrium (“LD”). The Office has interpreted this claim as being directed to the same invention as claim 2.

Claim 6: the language “further comprising determining the thrombomodulin sequence information for the subject” is considered indefinite.

Claims 10-15: the terms “decreased likelihood” in claim 10 (pertinent to claims 10-12), “increased likelihood” in claim 13 (pertinent to claims 13-15), and “less severe” in claim 14 are all relative terms which render the claims indefinite. The claims should make clear what “likelihood” would be considered increased or decreased, and with respect to what a comparison is made in determining “less severe” dysfunction.

Claims 13-15: the language “the protective genotype” in claim 13 (from which claims 14-15 depend) lacks antecedent basis.

Claim 16: indefinite for many reasons which are not repeated here

Applicants' Response

First, applicants note that the limitations of claims 10, 12 and 13 have been incorporated into claim 1, and the latter three claims are canceled. Claims 4, 15 and 16 have also been canceled. Hence, the rejection is moot with respect to claims 4, 10, 12, 13, 15 and 16.

Claim 1 has been amended so that there is now antecedent basis for all uses of “the” in the dependent claims (such as claims 2, 8, 14). Claim 1 now recites “protective genotype and “risk

genotype.” Moreover, there should be no question as to the meaning of the term “protective genotype.” See, for example specification at page 12, lines 1-10). Claim 6 is amended to remove any potential indefinite language.

Otherwise, Applicants contend that the meaning of the terms to which the rejection is targeted are known and understood by those of skill in the art. The Action questions the definiteness of “decreased/increased likelihood” and “less severe” despite the detailed description of clinical evaluation in the specification and the well established scoring criteria in the art, such as APACHE II (see for example, page 16, lines 16-22).

In view of the foregoing cancelations, amendments and explanations, it is believed that this ground for rejection may properly be withdrawn.

V. Rejections Under - 35 U.S.C. § 101

Claims 1-2, 4-6, and 9-17 were rejected as being directed to non-statutory subject matter.

{Applicants note that Claims 7 and 8 were free of this rejection; this rejection is moot with respect to the canceled claims.}

As characterized by the Office the claims are directed to a method “for obtaining a prognosis for a subject having, or at risk of developing, an inflammatory condition.” The method of independent claim 1 comprises a single step of

“determining a genotype of said subject at position 5318 or at position 4007 of SEQ ID NO:1, wherein said genotype is indicative of an ability of the subject to recover from the inflammatory condition”.

Two dependent claims included in this rejection recite additional steps: Claim 5 (now canceled) required “comparing” the determined genotype with known genotypes Claim 6 required “determining the thrombomodulin sequence information for the subject”. Claim 9 further provided a list of techniques that may be used to “determine” the genotype, among which was included “**reading sequence data**” which allegedly does not require a manipulative step(though the other alternatives require manipulative steps).

Claims 7-8 are noted as not being rejected as they provide further limitations that allow them to qualify as patent-eligible subject matter under § 101. These claims require that the determining be “performed on a nucleic acid sample from the subject” (claim 7) and further that a nucleic acid sample be obtained from the subject (claim 8).

The Office then relies on claims 7, 8 and 9, as a basis for concluding that claim 1 does **not require any** physical use or manipulation of a subject's nucleic acid, but rather embraces non-manipulative steps (such as "merely reading or otherwise ascertaining the identity of a subject's genotype without in fact performing any active or manipulative steps to accomplish 'determining'").

The Office has concluded that, the methods of the rejected claims are **not patent-eligible because** they fail the "machine-or-transformation test" (citing in a number of appellate decisions not repeated here). Because the rejected claims embrace both statutory and non-statutory embodiments, the Office states that they "must be rejected under 35 USC 101" as being directed to non-statutory subject matter. In conclusion, claims 1-2,4-6, and 9-17 allegedly do not qualify as patent-eligible process claims.

The "comparing step of claim 5 *{canceled, moot}*, does not require any type of physical manipulation, and therefore similarly fails both elements of the "machine or transformation" test. The "determining" of claim 6 allegedly encompasses both manipulative and non-manipulative "determining," and is therefore also rejected. *{amended to leave only manipulative step}* The rejection of claim 9, particularly applies to embodiment (i) of that claim. *{That embodiment is canceled.}*

Applicants' Response

The rejection of claims now canceled is moot. In claim 9, the indicated embodiment has been deleted, mooting the rejection of that claim.

Applicants disagree with the analysis, *e.g.*, of claim 1. Claim 1 has been amended to correspond almost perfectly to a claim recently allowed in a patent application from the same applicants (USSN 10/515,493) examined in the same Art Unit, but directed to establishing prognoses using single nucleotide polymorphisms (abbreviated herein as "SNPs") in another gene (Protein C) (see Appendix A submitted herewith.) Applicants believe that, similarly, there would be no reason to reject currently amended claim 1 under § 101.

Even though Applicants urge that an amendment is not necessary to render claim 1 patent-eligible under § 101, they are nevertheless *also* incorporating the language from claim 7 into claim 1. Since claim 7 was found to pass the tests under § 101, the presence of this language in claim 1 (using a nucleic acid sample from the subject to perform the genotype determination) could not possibly run afoul of § 101. Moreover, all the rejected claims include only "manipulative" steps.

It should be noted that the “machine-or-transformation test” is not to be considered exclusive or determinative and is only one factor in the § 101 analysis based on the recent Supreme Court decision in *Bilski and Warsaw v. Kappos* and the Office’s Revised Guidelines.

In view of the amendment of claim 1 and the foregoing discussion, this ground for rejection should be withdrawn for claim 1 and all claims dependent therefrom.

VI. Rejections Under 35 USC § 112, first paragraph (Enablement)

All pending claims, 1-2 and 4-17, were rejected as failing to comply with the enablement requirement. As characterized by the Office, the method of independent claim 1 (from which all claims depend) comprises a single step of

“determining a genotype of said subject at position 5318 or at position 4007 of SEQ ID NO:1, wherein said genotype is indicative of an ability of the subject to recover from the inflammatory condition”.

Accordingly, enablement would require that a genotype as determined in claim 1 allow one to obtain a prognosis for an “inflammatory condition.”

Dependent claims 10-15 recite further characteristics of risk genotypes and protective genotypes and their relationships with particular conditions, and claims 16- 17 further recite particular “inflammatory conditions” (claim 16 including “vast and disparate” types of conditions that are embraced by the term “inflammatory condition.”

The Office contends that the specification explicitly excludes “myocardial infarction” from being considered as an “inflammatory condition” embraced by the claims (based on the disclosure at page 9, lines 6-7 of the specification).

{Applicants note the foregoing contention is not relevant to the claims as presently limited.}

The specification discloses that position 4007 of SEQ ID NO:1 corresponds to a thrombomodulin gene polymorphism C1418T that is well-known in the art (*e.g.*, pages 3-4 of the specification and discussion “of prior art,” below).

{Applicants note the this characterization of “prior art” does not mean that it is being applied against the claims under either §§ 102 or 103, as it is not.}

The Action specifically points to a number of specific statements in the specification (at the indicated locations).

- prior findings of associations between the C1418T polymorphism and “various thrombotic events and cardiovascular disease have been “inconsistent” and “uncertain” (page 4, final paragraph). *{not applicable to amended claims}*
- Applicants own assays were conducted on haplotypes including a SNP at position 5318 of SEQ ID NO:1, which is disclosed as being in LD with the SNP at position 4007 (pages 5-6, particularly bottom of page 6).
- the “risk genotype” of the invention “may include at least one A nucleotide at position 5318 or at least one C nucleotide at position 4007 of SEQ ID NO:1” (at page 7).

{Indeed, claim 1(b)(i) recites these two genotypes as being risk genotypes that are “prognostic of a decreased ability to recover” (from the very limited set of inflammatory conditions) “or an increased likelihood of a poor outcome...”}

- These “risk” genotypes are reiterated at pages 11-12 as are “protective genotypes” including 5318C and/or 4007T.

{Indeed, claim 1(b)(ii) recites these two genotypes as being protective genotypes that are “prognostic of an increased ability to recover” (from the very limited set of inflammatory conditions) “or a decreased likelihood of a poor outcome...”}

- Applicants consider the C allele of the known C1418T SNP to be associated with a prognosis/risk of poor outcome.

{Applicants do not understand the relevance of this to the present (or prior claims).}

- Linkage of the 4007 and 5318 polymorphisms was determined via prior art methods (page 38 and 40- 41; Figure 1).

{The LD between these sites is not believed to be applicable to the amended claims.}

- Applicants genotyped 3 SNPs (position 5318 and two others) in their analyses of patient outcome.
- At pages 8-9, a vast number of different “inflammatory conditions” are listed that are embraced by the claims; the list of claim 16 explicitly excludes “myocardial infarction” (as noted above).

{Claim 1 and its dependent claims are now limited to determining prognosis in subjects with SIRS, sepsis or septic shock}

In view of the foregoing, the Action asserts that it is unpredictable as to whether one of skill in the relevant art could actually practice the claimed methods.

{See Applicants' more detailed remarks below.}

- Applicants report successful genotyping and analysis of 223 Caucasian patients with at least 2 of 4 SIRS criteria (pages 41-42). Haplotypes including 5318C were found to be “protective,” while individuals possessing the 5318A allele were found to be “1.95 times more likely to have a poor outcome....after adjusting for gender, age, and surgical diagnosis”.

{This comports with amended claim 1, et seq.; see remarks below.}

- In a separate analysis of the 5318 allele, the specification states that the 5318 C allele “appeared to be associated” with lower 28 day mortality (Fig 3) (page 43, lines 5-6)

{Accordingly, claim 1 states that 5318 C is a protective genotype.}

and that 5318A was found to be significantly associated with 28 day mortality in a subgroup of SIRS patients that had sepsis or septic shock (pg 43, lines 15-22; referencing Fig 5).

{Accordingly, claim 1 states that 5318 A is a risk genotype.}

- In the larger 223 patient cohort, as well as in the sepsis subgroup, the 5318A allele was associated with a more vigorous inflammatory response and fewer days alive and free (‘DAF’) of different SIRS criteria (page 43, lines 24-34).

{Accordingly claim 1 states that 5318 A is a risk genotype.}

- At page 44, lines 1-14, the specification discloses an association between the supposedly “protective” 5318C allele fewer DAF of cardiovascular failure and vasopressors (referencing Figure 6, although Figure 6 itself appears to contradict these statements).

{This apparent contradiction, due to a clerical error in the specification, is discussed below; this error is being corrected by amendment}

- Page 44 also reports associations between the 5318A and fewer DAF of respiratory failure, ventilation, hematologic system failure, neurologic dysfunction, and hepatic dysfunction. However, the specification also states that “When analyzed individually, there were no

significant associations between ...A5318C... and 28-day mortality or multiple organ system failure” (noted in the Office Action, at page 15, lines 13-14).

{A5318C does not belong in the category of “no significant association” and its inclusion in the specification here was a clerical error, corrected by the present amendment to the specification. There is ample support on pages 43 and 44 and in Figures 5 and 6 for a significant association between A5318C and 28-day mortality and DAF of both cardiovascular and respiratory dysfunction.}

Thus, the specification allegedly reports limited and contradictory findings with regard to one small group of human subjects exhibiting SIRS, a subset of whom have sepsis.

{These apparent contradictions are explained and corrected herein.}

Additionally, the specification is silent with regard to any evidence of associations between either allele of the claims and the vast majority of inflammatory conditions embraced by the claims in any type of subject.

{Claim 1 and its dependent claims are now limited to determining prognosis in human subjects with SIRS, sepsis or septic shock.}

The Office Action goes on to discuss several references that purportedly characterize the state of the art when this invention was made. Dahlman *et al.*, 2002, (“**Dahlman**”) allegedly suggest that the number of subjects assayed by Applicants is inadequate to conclude that a true genetic association is present (citing the entire reference). Accordingly, given the guidance provided in the specification, in view of the state of the art at the time the invention was made, one skilled in the relevant art would not have concluded that the claims under consideration were enabled. The prior art is allegedly silent about established correlations between the SNPs at position 5318 and any prognosis for “any inflammatory condition” embraced by the claims.

As for the SNP at 4007 (separately embraced by the claims), the prior art allegedly provides contradictory findings that would not allow a skilled artisan to conclude that any embodiments embraced by the claims may be successfully practiced.

One example of this in the Action is as follows: The Action earlier noted that myocardial infarction (“MI”) is not embraced by the claims, and now states that the prior art as exemplified by Konstantoulas *et al.* (2004, cited in IDS) summarizes the state of the art with regard to the two alleles at position 1418 of thrombomodulin (C1418T) and their association with risk of MI at the time the present invention was made, stating that “both or neither” variant have been reported to be

associated with MI in the prior art (page 628, left column). Thus, **Konstantoulas** allegedly makes clear that findings reported when attempting to assay the significance of that particular SNP with respect to another disease/condition have been confusing and contradictory (in confirmation of applicant's own teachings in the specification regarding the state of the art).

*{Applicants' apparent contradiction is discussed above and below.
Applicants do not understand the relevance of the discussion of 1418 to the present (or prior) claims; moreover, present claim 1 is limited to a very short list of inflammatory conditions and do not read on MI.*

The Office Action additionally cited Aleksic *et al.* (2003) which, failed to find an association between either allele of the 1418 SNP and venous thromboembolism or thrombosis after assaying a much larger group of cases and controls than was done by Applicants (citing to entire reference).

The foregoing led to the Office's position that

- (a) the prior art does enable Applicant's claims;
- (b) earlier studies of the 1418 SNP led to conflicting results;
- (c) there is a "particular need to replicate any findings before drawing conclusions regarding associations between this polymorphism and any disease/condition or patient prognosis."

{Applicants disagree with the foregoing, particularly point (c) as regards the present specification and claims}

The Office's enablement analysis concluded that given the high level of skill the art, it clearly within the ability of such an artisan to experiment further to determine whether actual correlations or associations exist between either of the alleles embraced by the claims and various types of "inflammatory conditions." However, the Office contends that the outcome of such experimentation is completely unpredictable, so that in the absence of evidence at the time the invention was made that any such associations actually exist,

...it is possible that even an infinite quantity of experimentation would not result in enablement of any methods embraced by the present claims. As such a type and quantity of experimentation is clearly undue, enablement is lacking...

The Action adds that the application lacks enablement even for human subjects and for SIRS and sepsis as inflammatory conditions *{without adequate basis in Applicants' view}*. Given this alleged deficiency, there is clearly insufficient enablement for "the numerous other types of subjects and conditions embraced by the claims."

Applicants' Response

In addition to Applicant's "briefer" comments above, the following is their more detailed response.

Applicants have amended claim 1 to limit the subject to a human and the inflammatory condition to SIRS, sepsis and septic shock. These inflammatory conditions are defined as follows in the specification, at page 22, lines 5-12:

A "systemic inflammatory response syndrome" or (SIRS) is defined as including both septic (i.e. sepsis or septic shock) and non-septic systemic inflammatory response (i.e. post operative). "SIRS" is further defined according to ACCP (American College of Chest Physicians) guidelines as the presence of two or more of A) temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$, B) heart rate > 90 beats per minute, C) respiratory rate > 20 breaths per minute, and D) white blood cell count $> 12,000$ per mm^3 or $< 4,000$ mm^3 . In the following description, the presence of two, three, or four of the "SIRS" criteria were scored each day over the 28 day observation period.

"Sepsis" is defined at page 22 (lines 14-16) as the presence of at least two "SIRS" criteria and known or suspected source of infection. Septic shock was defined as sepsis plus one new organ failure (by Brussels criteria) plus need for vasopressor medication.

Moreover Applicants bring to the Examiner's attention a publication by Bone *et al.* (hereinafter "**Bone**") ("Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis," The ACCP/SCCM Consensus Conference Committee: *Chest* (1992) 101:1644-55) which was the result of the work of Consensus Conference Committee of the American College of Chest Physicians/Society of Critical Care Medicine on sepsis and organ failure (copy and IDS submitted herewith). Bone defines "sepsis" at page 45, as being the same as the definition provided at page 22 of the specification. Bone defines "severe sepsis" and "septic shock" in a way that those skilled in the art would consider them encompassed by SIRS. For example:

- (i) "severe sepsis" is sepsis with organ dysfunction, hypoperfusion, or hypotension and
- (ii) "septic shock" is sepsis induced with hypotension despite adequate fluid resuscitation along with perfusion abnormalities).

It would appear that anyone with sepsis or undergoing septic shock suffers from SIRS as they would have to have at least two of the four SIRS criteria. Furthermore, the exemplary section of the specification, for example, page 37, line 22 through page 40, line 6) refers to (and provides data for) patient populations using the terms "Septic SIRS" (*e.g.*, pg 37, line 22) and alternatively (in Tables 2-4,) as "Sepsis SIRS."

As regards the Office's finding of "contradictions" in the disclosure, Applicants note that a typographical error (amended herein) at page 44 (first paragraph) of the specification may be the

source of the Office's (mis)understanding that this disclosure and Fig. 6 are contradictory. Line 2 was intended to read: "The 5318 C allele was significantly associated with more (*not fewer*), DAF of cardiovascular failure... That this was a clerical error is supported by the consistency of the corrected language with the remainder of the specification and drawings. Later in this paragraph it is stated that "The 5318 A allele was associated with fewer DAF of respiratory failure, ventilation, hematologic failure, neurologic and hepatic dysfunction - showing clearly that 5318A is , *i.e.*, Figure 6 (which shows at the patients enjoyed significantly more "days alive and free" of disease (DAF) with allele C than with allele A. Throughout (except for this one inadvertent error), the specification discloses that 5318A is the "risk genotype" whereas 5318C is the "protective genotype."

With regard to Office's reliance on the **Dahlman** reference, Applicants disagree with the contention that (1) a failure to "report findings in any other population" and (2) "such replication is considered in the relevant art to be a standard step that should be taken before concluding that any association of the type claimed herein is significant." As with any scientific inquiry there may be criticism lodged against a given method, but that does not undermine the value of the method and is certainly not the standard to be applied when determining enablement.

In citing **Dahlman**, it appears that the Office objects to the data in the present application as not properly correlated with the claimed subject matter. Correlation generally relates to the presence or absence of working examples, and specifically the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. Data from an *in vitro* or *in vivo* animal model in the specification may constitute a "working example" if the data "correlates" with the claimed method. (The data might not be viewed as a "working example" in the absence of correlation). Furthermore, if the art recognizes that a particular model is correlated with a specific human condition, then it should be accepted unless the Examiner can provide evidence that the model does not correlate. Nevertheless, an Examiner is obligated to consider the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)(reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). A rigorous or an invariable exact correlation is not required (*Cross v. Iizuka* , 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

...based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

Accordingly, even if the present invention were based on *in vitro* data or *in vivo* data in an animal model system, which it is not, the Office's evident requirement that the working examples rise to a "**Dahlman** standard" is inconsistent with the legal requirement that a correlation between the data and the claimed method be reasonably based upon the probative evidence. Applicant contends that the data in the present application is reasonably correlated with the claimed methods.

Applicants findings as they appear in the application provide an enabling disclosure for the claims as presently amended, without need for reliance on outside documents. Applicants sense that some of the Office's analysis of the cited references appears to be in the nature of "scientific refereeing" of a paper submitted for publication rather than a proper (legal) enablement analysis under § 112. There is no basis for doubting Applicant's data and conclusions therefrom that support the present claims. The occurrence of the indicated "internal contradictions" stemming from clerical errors has been explained and corrected. The sum of Applicants' disclosure provides legally adequate enabling support for the present claims. Applicants therefore request withdrawal of this ground of rejection.

VII. CONCLUSION

Applicants respectfully request entry of the amendments and remarks and reconsideration of the rejections. The claims are now believed to be in condition for allowance.

The Examiner is invited to phone the undersigned at the number shown below if that would assist in further examination of this case.

Respectfully submitted,

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